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To: C. Linsky

Re: Cytotoxicity Risk Assessment for the TVT (Ulmsten) Device

A number of in vitro cytotoxicity studies were conducted to assess the cytotoxic potential of the components of the Ulmsten device as part of an overall assessment of biocompatibility (Attachment 1). The device consists of two stainless steel needles, a polyethylene (PE) sheath, heat-shrink tubing (connects mesh and sheath to needle), two PE needle guards, and a strip of polypropylene (PP) mesh. The needles, heat-shrink tubing, and the PE sheath have relatively brief contact with the patient while the PP mesh is permanently implanted in the body. The PE needle guards are used to prevent the needles from damaging the packaging and do not come in contact with the patient.

The testing was conducted at different locations using testing protocols that varied in some important aspects such as extraction conditions and scoring systems. After an evaluation of all the test results, the components of the Ulmsten device that were considered to be "noncytotoxic" were the needle, PE needle guard, heat-shrink tubing, and PE sheath. Overall, there is some evidence to suggest that the PP mesh from the sterile Ulmsten device may have cytotoxic potential. However, the raw material PP mesh was considered to be noncytotoxic.

The assessment of biocompatibility of a medical device must take into consideration all available data including clinical data which is the most relevant. In this case, there is abundant clinical data (around 1000 patients including over 200 documented cases) which demonstrates that the Ulmsten PP mesh strip implanted in the body to control urinary stress incontinence has fewer complications in terms of tissue reaction than other comparable devices. This suggests that any potential irritancy of the PP mesh after implantation is self-limiting and minimal when compared to the implantation procedure itself. Thus, this clinical data provides important evidence that the cytotoxicity of the PP mesh observed in vitro does not translate into any clinical significance or adverse patient outcomes.

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Attachment 1

Summary of Cytotoxicity Testing

1. Scantox Study

The initial cytotoxicity testing of the finished Ulmsten device was conducted by Scantox (Lab No. 22806) for Medscand Medical AB during March 10-13, 1997. This testing was limited to an ISO Elution test of the heat-shrink tubing (3 cm^2/ml including both sides) and PE sheath (6 cm^2/ml including both sides) components after extraction together for 24 hours at 37 °C. The results (on the USP scoring scale of 0 to 4) indicated that the extract was severely (grade 4) cytotoxic. These test results are considered inconclusive because the extracts of these materials were tested together.

2. Ethicon, Scotland Studies

A series of cytotoxicity experiments were then conducted by Ethicon, Scotland (Interim Report 15/97) during early May, 1997 to expand on the results from the Scantox study. The results (on an internal scoring scale of 0 to 3) of the ISO Elution test of the sterile Ulmsten device components extracted for 24 hours at 37 °C were as follows:

Needle (0.1 g/ml) - Noncytotoxic
Heat-shrink tubing (0.1 g/ml) - Marked cytotoxicity
PE sheath (3 cm^2/ml [includes only one side]) - Slight cytotoxicity
PP mesh (3 cm^2/ml [includes only one side]) - Marked cytotoxicity

In addition, cytotoxicity testing was conducted under similar conditions on sterile and nonsterile samples of PP mesh used in the construction of the Ulmsten device. The results indicated that these PP mesh samples also had marked cytotoxicity.

The results of ISO Agar Overlay test (on an internal scoring scale of 0 to 3) of the device components were as follows:

Heat-shrink tubing - Moderate cytotoxicity
PE sheath - Slight cytotoxicity
PP mesh - Marked cytotoxicity

3. BIOLAB, Italy Studies

Further cytotoxicity testing of the sterile Ulmsten device was conducted by BIOLAB, Italy (Report Nos. 97/8053-1, 97/8053-2, 97/8053-3) in early June, 1997. The results (on a USP

scoring scale of 0 to 4) of the ISO Elution test of the device components extracted (by weight) for 72 hours at 37 °C were as follows:

Heat-shrink tubing (0.2 g/ml) - Noncytotoxic
PE sheath (0.2 g/ml) - Slight cytotoxicity
PP mesh (0.2 g/ml) - Noncytotoxic

4. NAmSA, U.S. Studies

Final testing of the sterile Ulmsten device was conducted by NAmSA, U.S. (PSE 97-0128) in early July, 1997 to provide cytotoxicity results from a laboratory which has been used reliably by Ethicon, Inc. for a number of years to support regulatory submissions and for which there is a baseline of cytotoxicity data for a number of our products. The results (on a USP scoring scale of 0 to 4) of the ISO Elution test of the device components extracted for 24 hours at 37 °C were as follows:

Heat-shrink tubing (3 cm^2/ml [includes both sides]) - Noncytotoxic
PE sheath (6 cm^2/ml [includes both sides]) - Noncytotoxic
PE needle guard (3 cm^2/ml) - Noncytotoxic
Needle (0.2 g/ml) - Noncytotoxic
PP mesh (3 cm^2/ml [includes both sides, 33 mg/ml]) - Severe cytotoxicity

The results of ISO Agarose Overlay testing for the device components were as follows:

Heat-shrink tubing - Noncytotoxic
PE sheath - Noncytotoxic
PP mesh - Noncytotoxic

In addition, ISO Elution cytotoxicity testing was conducted under similar conditions at NAmSA on two of the same nonsterile samples of PP mesh which resulted in marked cytotoxicity in tests conducted at Ethicon (Scotland). The results (PSE 97-0122 and 97-0123) indicated that these PP mesh samples were noncytotoxic.

Discussion

To gain a broader perspective of the cytotoxicity of PP devices in general, elution cytotoxicity studies were also conducted with Bard Marlex PP mesh (PSE 97-0118) and Surgilene PP suture (PSE 97-0119). The results indicated that these PP devices were noncytotoxic. Also, Ethicon, Inc. conducted agarose overlay and elution cytotoxicity tests with normal production sterile PROLENE (polypropylene) mesh at NAmSA in 1993 (PTS 92-1411) which indicated that this PP mesh was noncytotoxic in both cytotoxicity test systems. It should be noted that PP is often used in cytotoxicity testing as a negative control as it was in the first study conducted by Scantox.

Some of the apparent conflicting test results from the different testing facilities can be addressed by understanding that slightly differing testing protocols were followed. Although all the testing was described as conforming to ISO 10993-5 guidelines entitled "Biological Evaluation of Medical Devices - Tests for Cytotoxicity: In Vitro Methods", there were some technical differences relating to the extraction procedures, all within the broad guidelines of this standard, which may have influenced the final outcomes.

For example, USP extraction conditions state that both sides of a two-dimensional sample (e.g. mesh) be included in the calculation of surface area for extraction. Since Ethicon (Scotland) used only one side in the calculation of surface area, they effectively doubled the amount of material extracted compared to the testing conducted at NAmSA. Thus, the test results from NAmSA for the samples of raw material PP mesh used in the construction of the Ulmsten device indicating no cytotoxicity were considered to most appropriately reflect the potential cytotoxicity of this material.

Using the USP acceptability criteria for cytotoxicity to be a grade of no more than mild (Grade 2) cytotoxicity, the components of the Ulmsten device found to be "noncytotoxic" were the needle, PE needle guard, and PE sheath. The heat-shrink tubing was found to be noncytotoxic by NAmSA and BIOLAB. The moderate to marked cytotoxicity of the heat-shrink tubing reported by Ethicon (Scotland) may be a reflection of the different scoring system and/or the increased sensitivity of the test systems. However, based on the weight of the evidence, the heat-shrink tubing was considered to be noncytotoxic.

The PP mesh component of the Ulmsten device was cytotoxic in only the Elution test reported by NAmSA and in both test sytems reported by Ethicon (Scotland). The noncytotoxic result reported from BIOLAB is not clearly understood. Although the extraction conditions were exaggerated (200 mg/ml versus 33 mg/ml and 72 hours versus 24 hours), no information is available on the stability of this extract over time. Overall, there is some evidence to suggest that the PP mesh from the sterile Ulmsten device may have cytotoxic potential.

Conclusion

An assessment of the biocompatibility of a medical device must take into consideration all available data, including clinical data which is the most relevant, rather than focus on individual test results. In this case, there is abundant clinical data (around 1000 patients including over 200 documented cases) which demonstrates that the Ulmsten PP mesh strip implanted in the body to control urinary stress incontinence has fewer complications in terms of tissue reaction than other comparable devices. This suggests that any potential irritancy of the PP mesh after implantation is self-limiting or minimal when compared to the implantation procedure itself. Thus, this clinical data provides important evidence that the cytotoxicity of the PP mesh observed in vitro does not translate into any clinical significance or adverse patient outcomes.

